CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

ALKYL ($C_{10 - 16}$) DIMETHYL AMINE OXIDE

Chemical Code # 3896, Tolerance # 52538

8/3/99

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap; no adverse effect
Chronic toxicity, dog:	No study on file[1]
Oncogenicity, rat:	No study on file[1]
Oncogenicity, mouse:	Inadequate study; no adverse effect indicated[1, 2]
Reproduction, rat:	No study on file[1]
Teratology, rat:	Data gap; inadequate study; no adverse effect indicated
Teratology, rabbit:	No study on file[1]
Gene mutation:	Data gap; inadequate study; no adverse effect indicated
Chromosome effects:	Data gap; inadequate study; no adverse effect indicated
DNA damage:	Data gap; inadequate study; no adverse effect indicated
Neurotoxicity:	No study on file[1]

Toxicology one-liners are attached.

All record numbers through 163366 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect.
indicates a study on file but not yet reviewed.
File name: T175667
Leung, 8/3/99

[1] New active ingredient, Alkyl ($C_{10 - 16}$) Dimethyl Amine Oxide, submitted as an antimicrobial for terrestrial non-food use. These studies are not required at this time.

[2] This study was submitted because the skin was determined to be a potential route of exposure.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

CHRONIC, RAT

** 52538-012; 163362**;** "Two-Year Rat Feeding Study" (C.W. Cardin et. al., International Research & Development Corporation, Mattawan, MI, Study # 191-408, 4/4/83). P0571 (Dodecyl Dimethyl Amine Oxide, 27% a.i.) was administered orally in the diet to 60 CD rats/sex/dose at concentrations of 0, 0.01, 0.1, and 0.2% a.i. for two years. An additiol group of 30 rats/sex were included as a second control group to be used only in the event of early termition resulting from low survival. No treatment-related changes in clinical signs, differences in survival, hematology, urilysis or clinical chemistry were reported. However, reduction in body weights were noted in high dose rats (males: 87.7% of control, $p < 0.05$; females: 85.7% of control, $p < 0.05$) with deceased food consumption. Body weight losses were also observed in low and mid dose males at weeks 52, 65 and 78 (93.1 to 94.8% of control, $p < 0.05$), but were comparable to controls at 104 weeks. Eye lesions (kerititis, cataract) were observed during ophthalmological and histopathological examitions were not considered to be treatment-related because these types of lesions are normally associated with aging, the lack of bilateral involvement, and the lack of consistent progression of lens disease as the rats were continuously treated with the test material. **No adverse effects**. NOEL (M/F) = 0.1% (M: 42.3 mg/kg; F: 52.6 mg/kg; based on body weight reduction). **Acceptable**. (Leung, 7/6/99).

[This study was published in Fundamental and Applied Toxicology 5: 869-878, 1985].

CHRONIC TOXICITY, DOG

No study submitted

ONCOGENICITY, RAT

No study submitted

ONCOGENICITY, MOUSE

52538-012; 163362; "Toxicological Evaluation of Commercial Alkyldimethylamine Oxides: Two-year Chronic Feeding and Dermal Studies" by C.W. Cardin et. al., published in Fundamental and Applied Toxicology 5: 869-878, 1985. Note: results from the feeding study was also submitted in a separate study report (see record # 163362, document 52538-012). 75 ICR Swiss mice (CD-1)/sex/dose were exposed to ADAO via dermal application of 0.1 ml of an aqueous solution of ADAO at concentrations of 0, 0.05, 0.13, or 0.26% w/v ADAO [adjusted to 100% a.i.] once daily three times per week for 104 weeks. An additional group of 45 mice/sex were included as a second control group to be used only in the event of early termination resulting from low survival. This contingent group was not needed in this study. No skin tumors were observed at the treatment site in any group. There were no compound-related skin or systemic neoplasm noted. Compound-related dermal irritation (diffuse acanthosis and hyperkeratosis) was observed in treated skin sections from high dose mice during histopathological examination. There were no significant differences between male and female mice in the incidence of skin irritation. Dermal NOEL M/F) = 0.13% (based on dermal irritation), systemic NOEL not determined. **Supplemental**; (Leung, 8/2/99).

REPRODUCTION, RAT

No study submitted

TERATOLOGY, RAT

011; 163356; "Effect of E9076 on Pregnancy of the Rat"; (D.D. Conzens, *et. al.*; Huntingdon Research Centre, Huntingdon, Cambridgeshire, UK; Project ID. ECM BTS 272S1; 4/15/81); Twenty pregnant female Sprague-Dawley rats were dosed orally by gavage from day 6 through day 15 of gestation with 0, 6.0, 18.0 or 54.0 mg/kg/day of E9076. No mortalities among the dams resulted from the treatment. Increased salivation was noted for the dams in the high dose immediately after dosing. There was no treatment-related effect on food consumption nor body weight gain. Necropsy of the dams did not reveal any treatment-related lesions. There were no treatment-related effects upon post-implantation loss or litter weight. One fetus in the high dose group exhibited vertebral agenesis. However, this malformation was judged not to be treatment-related. Otherwise, there were no treatment-related anomalies noted. **No adverse effect indicated. Maternal NOEL:** 18 mg/kg/day (based on increased salivation after dosing noted in the 54.0 mg/kg/day treatment group); **Developmental NOEL:** 54.0 mg/kg/day (HTD); **Supplemental Study** (test material chemically different from the active ingredient under consideration)**.** (Moore, 7/8/99)

TERATOLOGY, RABBIT

No study submitted

GENE MUTATION

011; 163358; "Studies of *In Vitro* Cell Transformation and Mutagenicity by Surfactants and Other Compounds"; (K. Inoue, *et. al.;* Biological Research Section, Tochigi Research Laboratories, Kao Soap Co., Ltd, Tochigi 321-34, Japan and Department of Experimental Pathology, Cancer Institute, Tokyo 170, Japan; Food & Cosmetics Toxicol. 18, pp. 289 to 296 (1980)); The genotoxicity of two alkyl dimethyl amine oxides, (1) N,N-dimethyldodecylamine oxide, (2) N,N-dimethyltetradecylamine oxide, was evaluated in two *in vitro* assays, hamster embryo cell transformation assay and Ames' mutagenicity assay. In the former test, (1) was incubated at treatment levels ranging from 0.1 to 20 µg/ml in three different cultures for 8 days at 37^{o} C. Likewise, (2) was incubated under the same conditions at treatment levels ranging from 0.1 to 10 µg/ml. The incubations were done in triplicate. There was no apparent treatment-related effect upon the transformation of these cells. However, the response of the positive control, 3-methylcholanthrene, was minimal as well. The significance of the assay results are questionable. In the Ames' mutagenicity test, the two test materials were preincubated for 20 minutes and then incubated for 48 hours at 37^{o} C with *Salmonella typhimurium* strains TA98 and TA100 at concentrations ranging from 10 to 200 µg/plate under conditions of non-activation and activation. The S9 fraction used for the metabolism of the test materials was procured from the livers of rats pretreated with polychlorinated biphenyl. Neither of the test materials demonstrated a treatment-related increase in reversion mutation. In this assay, the positive controls adequately demonstrated the validity of the assay. **No adverse effect indicated. Summary Report.** (Moore, 7/8/99

CHROMOSOME EFFECTS

011; 163359; "The Evaluation of Dimethyl Dodecylamine Oxide (UDX-7577) in the Dominant Lethal Assay"; (C.J. Harris and K.M. Pieper; The Proctor & Gamble Company, Research and Development Department, P&RS Division, Cincinnati, OH; no report no.; 10/1/75); Twenty male C3D2F1/J mice/group were treated orally with 0 (water), 10, 100 or 1000 mg/kg/day with UDX-7577 (a.i.: 27.7%) for 5 days. An additional group of males was not dosed. After dosing, each male was mated with two females/week for 7 weeks. Thirteen days after the presumptive mating (3 to 4 days after being first mated), the females were euthanized and uterine examinations were performed. There were no treatment-related effects upon the incidence of pregancy, the total number of implantations/pregnant female, the average number of fetal deaths/pregnant female, and the mutagenic indices. No appropriate positive control data were included. **No adverse effects indicated. Summary Report.** (Moore, 7/8/99)

DNA DAMAGE

See Gene Mutation above

NEUROTOXICITY

No study submitted

SUBCHRONIC STUDIES

52538-010; 163355; "Thirteen-Week Subchronic Dietary Administration to Male and Female Rats" (C. W. Cardin et. al., Hazleton laboratories America, Inc., Vienna, VA, Project # 297-329; 5/2/80). P0434 (27.72% a.i.) was administered orally in the diet to 20 Sprague-Dawley rats/sex/dose at 0, 0.1, 0.2 and 0.4% for 13 weeks. One mid dose male died during week 9. Reduced mean body weight was reported in high dose rats (weeks 1 through 13) and mid dose females (weeks 3 to 5 and 9 to 13) with decreased food consumption in mid and high dose rats. Elevated alkaline phosphatase was detected in all treated males and high dose females at week 13. **Possible adverse effect:** Ophthalmological examination revealed lenticular opacities in 3 mid dose males and the remaining 12 males and 8 females from the high dose. Necropsy and histopathology did not exhibit any treatment-related findings. No histological findings were reported in the eye at 0.4%. NOEL (M/F) = 0.1% (based on lenticular opacity and reduced mean body weight). **Acceptable**. (Leung 7/9/99).

METABOLISM STUDIES

013; 163365; "The Absorption, Tissue Distribution, and Excretion of Dodecyldimethylamine Oxide (DDAO) in Selected Animal Species and the Absorption and Excretion of DDAO in Man"; (D.P. Rice; The Proctor & Gamble Company, Sharon Woods Technical Center, Cincinnati, OH; Toxicol. Appl. Pharmacol. 39, 377-389 (1977)); Male rats were treated by oral gavage with 100 mg/kg of either (1) [methyl-^{14} C]DDAO (spec. act. 1.3 mCi/g) or (2) [1-dodecyl-^{14} C]DDAO (spec. act. 1 mCi/g). Female rats received the same dose of the latter radiolabeled test material. Urine, CO_2, and feces were collected for up to 72 hours for the males and 48 hours for the females. The urine was the predominant path of excretion ((1) males: 71%, (2) males: 53.5%, females: 53.6%). Excretion as $^{14}CO_2$ was enhanced with the radiolabel on the alkyl chain of (2) (23.1% vs. (1) 13.1% of the administered dose). In this circumstance, recovery in the urine was similarly reduced for (1). Excretion in the feces constituted from 9.4 to 12.1% of the administered dose for either test material. The liver had the highest level of residue 72 hours after dosing (males: 1.1 to 1.25%, females: 1.48% of the administered dose). Administration of (1) intraperitoneally did not alter the excretion profile when compared to the orally administered compound. Bile duct-cannulation resulted in the recovery of approximately 3 to 4% of the administered dose in the bile. For two human subjects dosed orally with (2), urine was the predominant path of excretion, followed by excretion as $^{14}CO_2$, a profile similar to that of the rat. Very low levels were recovered in the feces. An interspecies comparison of percutaneous absorption was performed by applying DDAO to the skin of rats, mice, rabbits and humans. The doses applied ranged from 0.7 to 2.33 nmol DDAO/cm^2 with the greatest percentage of absorption demonstrated by the rabbit, followed by the rat, mouse and man. The transcutaneous flux of the test material ranged from 6.7 nmoles/hr/cm^2 for the rabbit (72 hour measure) to < 0.2 nmoles/hr/cm^2 for humans (8 hour measure). Although the study experienced some technical problems (feces and urine samples were cross-contaminated in the bile duct cannulation study, method of sampling for the human oral dosing study may have resulted in a failure to account for all of the radiolabel excreted), the data indicated that oral uptake and excretion of DDAO was rapid with removal by metabolism to CO_2 being an important pathway. Dermal uptake of DDAO was significantly less for humans as compared to other species. **Summary Report.** (Moore, 7/12/99)

013; 163366; "A Comparison of the Elimination and Biotransformation of

Dodecyldimethylamine Oxide (DDAO) by Rats, Rabbits, and Man"; (T.S. Turan and W.B. Gibson; The Proctor & Gamble Company, Miami Valley Laboratories, Cincinnati, OH; Xenobiotica 11, 447-458 (1981)); Rats, rabbits and humans were dosed orally with [1-^{14} C]DDAO (purity $\geq$ 98%) and the elimination of the radiolabel over at least a 48 hour period was determined. The dosages adminstered were as follows: (rat) 1, 100 mg/kg, (rabbit) 1 mg/kg, 37 to 57 mg/kg, (man) 0.7 mg/kg. The urine was the primary excretion pathway in all of the species (range: 43.9 to 65.7% of the dose). Elimination via CO_2 entailed 19.2 to 32% of the dose. Otherwise, radiolabel in the feces constituted only 2.5 to 9.4%. The label was largely excreted within the first 24 hours after dosing with recovery ranging from 75.2 to 87.9% of the total radiolabel recovered. Isolation of the metabolites in the urine identified (1) ? -oxidation to form carboxylic acids, (2) ß-oxidation, (3) hydroxylation of the alkyl chain, and (4) reduction of the amine oxide to the amine as primary pathways of metabolism. Rabbits and humans were apparently more efficient in degrading the alkyl chain than were the rats. None of the parent compound was isolated in the urine samples. **Summary report.** (Moore, 7/12/99)